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(54) Title: SUSTAINED RELEASE TABLET FORMULATIONS COMPRISING CLARITHROMYCIN

(57) Abstract: This invention covers the sustained release tablets containing hydroxypropylmethylcellulose as matrix material and clarithromycin as active ingredient. Clarithromycin is released from sustained release tablet with a rate expressed by the equation $M_t/M_\infty=kt^n$. In this equation n is the exponent of the release kinetics and n value determines the type of release mechanism. When n value is between 0.89 to 1, release rate complies with zero-order kinetic and it is independent from time.

SUSTAINED RELEASE TABLET FORMULATIONS COMPRISING CLARITHROMYCIN

The present invention is concerned with a sustained release pharmaceutical formulation containing clarithromycin as the active ingredient for oral administration.

Clarithromycin is a semi-synthetic macrolid antibiotic. Chemically, it is 6-O-methylerythromycin. The molecular formula of clarithromycin is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. J.P.Pat.No. 163,823/1985 indicates increased bioavailability of 6-O-methylerythromycin with citric acid.

Many different types of sustained release oral dosage forms have been developed, but each has some disadvantages which effect its suitability to a particular drug and therapeutic objective. Hydrophilic polymers, especially celluloses, are extremely popular in controlling the release rate of drugs from solid dosage forms. Their ease of compression, ability to accomodate large amounts of the drug, the minimum influence exerted by the processing variables on the release rate and relatively low cost are the main reasons for their advantages.

Hydroxypropylmethylcellulose (HPMC) is most widely used in matrix tablets and other types of sustained-release dosage forms because of its characteristics, namely, non-toxic nature of polymer, its capacity to incorporate active ingredients, manufacture of tablets by direct compression or wet granulation and pH independence.

An effective way to reduce the fluctuation of plasma blood levels is to deliver the drug in a dosage form which results in zero order absorption kinetics. Assuming that the release rate is the rate-limiting step for drug arrival at the systemic circulation, the kinetics of the release process should be zero order.

Korsmeyer et. al. used a simple equation to describe drug release behaviour from sustained release polymer matrices.

$$Mt / M\infty = k\, t^n$$

or

$$\log Mt / M\infty = \log k + n \log t$$

Where Mt / M∞ is the fraction of the released drug, k represents a constant incorporating structural and geometric characteristics of the release device, and n is the diffusional exponent for the released drug. The value of n gives an indication of the release mechanism. When n value is between 0.89 and 1, the release rate is independent of time and this is a desirable mechanism in oral sustained drug delivery systems (U.S. Pat. No. 5,945,125)

U.S. Pat. Nos. 4,601,894 and 4,657,757 have disclosed controlled-release matrix dosage forms containing acetaminophen, dextrobrompheniramine maleate in a single homogenous mixture of of hydroxypropylmethylcellulose and ethers and other cellulose and cellulose ether derivatives.

U.S.Pat.No.4,571,333 have disclosed the use of hydroxypropylmethylcellulose as the carrier base for sustained release pharmaceutical tablets. In this study is directed to preparation of once a day controlled release tablets incorporating naproxen or naproxen sodium and 4 to 9 % hydroxypropylmethylcellulose in total tablet weight.

Sustained release indapamide tablets have been prepared by using hydroxypropylmethylcellulose in U.S.Pat. No. 5,334,392. In this study 50 percent of the total amount of indapamide is released linearly in more than eight hours between the period of 5 and 14 hours.

U.S. Pat. No. 5,705,190 have disclosed controlled-release dosage forms containing drug and organic acid in alginat formulation. In this invention controlled release clarithromycin tablets have been prepared by using alginate.

The present invention is concerned with the preparation of sustained release tablet formulations containing clarithromycin for oral administration and release of active ingredient from the tablet between 0 and 12 hours by zero-order kinetic.

DESCRIPTION OF THE DRAWINGS

Fig. 1 Dissolution profiles of an immediate release clarithromycin tablet and SRC I and SRC II coded tablets prepared according to the example 1.

Fig. 2 Dissolution profiles of an immediate release clarithromycin tablet and SRC III coded tablets prepared according to the example 2.

DESCRIPTION OF THE INVENTION

Methylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylcellulose, carboxymethylcellulose and carboxyethylcellulose or mixtures of them or mixtures of these polymers with hydroxypropylmethylcellulose are used as swellable polymer in the sustained release dosage forms.

Particularly HPMC USP 2910 and USP 2208 polymers which are mentioned in USP are used extensively. Among these polymers Methocel K100M, Methocel E4M, E15M are produced by the Dow Chemical Co. with these trade names. Here the designation 'E' refers to USP 2910 and the designation 'K' refers to USP 2208 wherein the number designations refer to the viscosity of the polymer in a 2% aqueous solution (e.g. 4M designates a viscosity of 4000 cps) and average molecular weight (E4M has molecular weight of 86,000, E15M has molecular weight of 120,000, K100M has molecular weight of 246,000).

EXAMPLE 1

The sustained-release clarithromycin tablets (SRC I an SRC II) were prepared according to the formula given in Table 1. The dissolution profiles of these tablets were tested and evaluated by using rotated paddle method given in USP test <711> in 900 mL pH 4 phosphate buffer at 37 °C and 50 rpm paddle rate.

Table 1 displays the preferred amounts of ingredients will be used for a sustained release clarithromycin tablet which is developed in this invention.

Table 1.

Unit Formula of the SRC I and SRC II Tablets

Composition	Unit formula SRC I (mg)	Unit formula SRC II (mg)
Clarithromycin	500	500
Citric acid	130	130
Hydroxypropylmethylcellulose*	70	80
Lactose	150	220
Stearic acid	20	20
Talc	30	30
Magnesium stearate	10	10

*Any high-viscosity hydroxypropylmethylcellulose can be employed, preferably having a viscosity between 1,000 and 20,000 cps. In this example the one having a viscosity 15,000 cps was used.

Preparation of the Tablet:

1. Clarithromycin, lactose, citric acid and hydroxypropylmethylcellulose are blended in a appropriate blending equipment.
2. The blended material obtained in stage 1 is granulated by using purified water. The granulated mass is passed through an appropriate screen.
3. The granulated material is dried until having moisture content of less than 4% by using moisture balance.
4. The dried granulated material is passed through screen having appropriate apertures.
5. The blended material obtained in stage 4 is lubricated by using talc, stearic acid and magnesium stearate.
6. The blended material is tabletted by using appropriate tablet machine.

EXAMPLE 2

The sustained-release clarithromycin tablets (SRC III) were prepared according to the formula given in Table 2. The dissolution profiles of these tablets were evaluated as described in Example 1.

Table 2 displays the preferred amounts of ingredients will be used for a sustained release clarithromycin tablet which is developed in this invention.

Table 2.

Unit Formula of the SRC III Tablets

Composition	Unit formula SRC III (mg)
Clarithromycin	500
Citric acid	130
Hydroxypropylmethylcellulose*	70
Microcrystalline cellulose	120
Stearic acid	20
Talc	30
Magnesium stearate	10

*Any high-viscosity hydroxypropylmethylcellulose can be employed, preferably having a viscosity between 1,000 and 20,000 cps. In this example the one having a viscosity 15,000 cps was used.

Preparation of the Tablet:

Clarithromycin, Microcrystalline cellulose, citric acid and hydroxypropylmethyl cellulose are blended in a appropriate blending equipment.

Beginning from the second stage, production method is the same as with the method given in Example 1.

Sustained release clarithromycin tablets developed in this invention can be produced by others with some additions or changes to reach the same results in different mixing ratios, However if these additions or changes are related with the components and knowledges of this description, they are evaluated in the content of this invention as varied applications of this invention.

CLAIMS

1. Sustained release clarithromycin tablets characterized in that it contains hydroxyalkylcellulose as a hydrophilic matrix material, pharmaceutically accepted excipients and lubricants.
2. Sustained release clarithromycin tablets according to claim 1 characterized in that the release from the tablet at a rate expressed as $Mt/M\infty = k\,t^n$ where n is the exponent of the release kinetics.
3. Sustained release clarithromycin tablets according to claims 1 and 2 characterized in that n is about 0.89 to 1.00 and due to this criteria the release mechanism is resulted in zero-order release kinetics.
4. Sustained release clarithromycin tablets according to claims 1,2 and 3, characterized in that at least 60 percent clarithromycin is released in 14 hours.
5. Sustained release clarithromycin tablets according to claims 1,2,3 and 4 characterized in that maximum 65 percent clarithromycin is released up to 8 hours.
6. Sustained release clarithromycin tablets according to claims 1,2,3,4 and 5 characterized in that the release of clarithromycin from the tablet up to 12 hours with zero-order kinetic.
7. Sustained release clarithromycin tablet according to claims 1,2,3,4,5 and 6 characterized in that the hydroxyalkylcellulose polymers are hydroxypropylmethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and mixtures of these polymers.
8. Sustained release clarithromycin tablets according to claims 1,2,3,4,5,6 and 7 characterized in that weight percent of clarithromycin in total tablet weight is 25 to 90.
9. Sustained release clarithromycin tablets according to claims 1,2,3,4,5,6,7 and 8 characterized in that weight percent of hydroxyalkylcelluloses or their mixtures in total tablet weight is 3 to 40.
10. Sustained release clarithromycin tablets according to claims 1,2,3,4,5,6,7,8 and 9 characterized in that citric acid, lactose and microcrystalline cellulose are used as pharmaceutically accepted excipients.
11. Sustained release clarithromycin tablets according to claims 1,2,3,4,5,6,7,8,9 and 10 characterized in that weight percent of lactose in total tablet weight is 5 to 50.

12. Sustained release clarithromycin tablets according to claims 1,2,3,4,5,6,7,8,9,10 and 11 characterized in that weight percent of microcrystalline cellulose in total tablet weight is 5 to 50.

13. Sustained release clarithromycin tablet according to claims 1,2,3,4,5,6,7,8,9,10,11 and 12 characterized in that the lubricants are talc, magnesium stearate, stearic acid or mixtures of them.

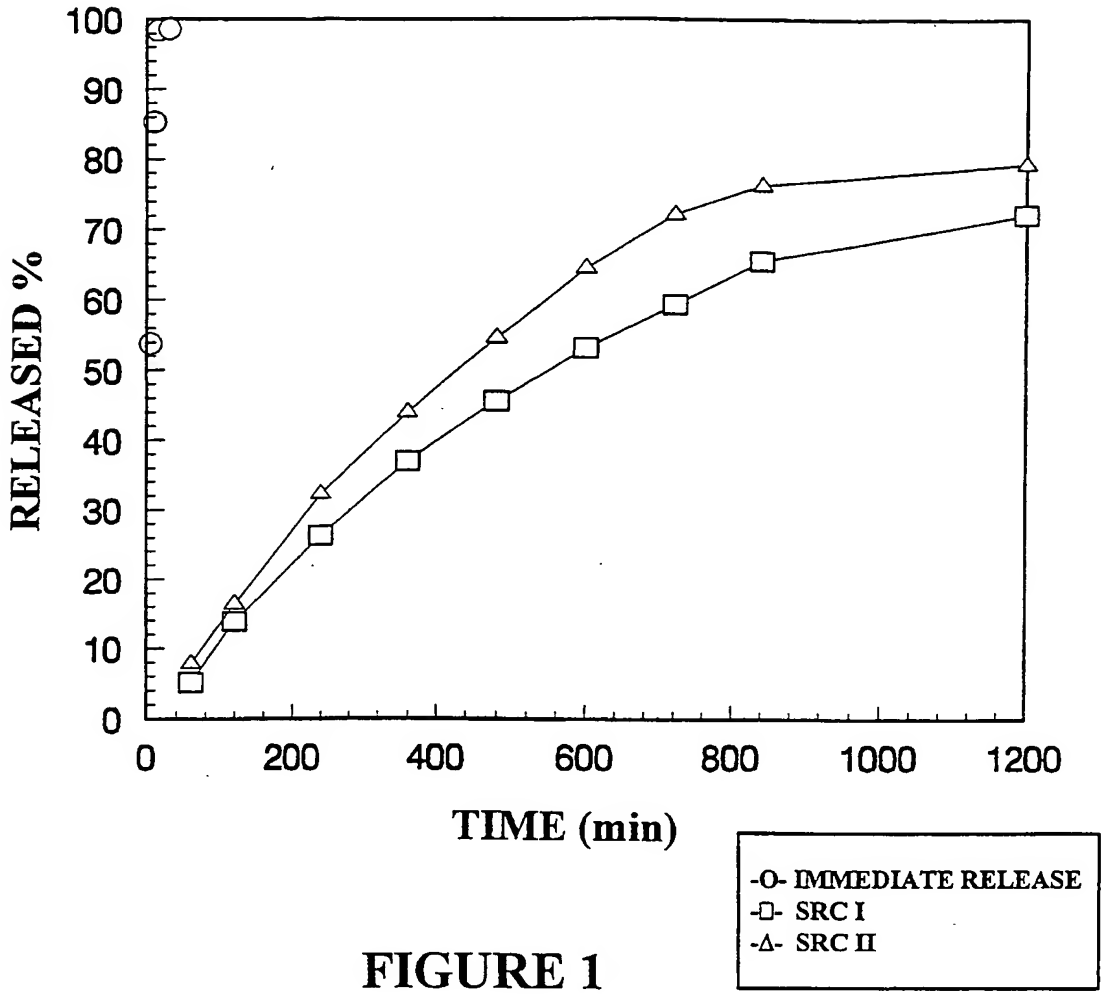
100
90
80
70
60
50
40
30
20
10
0
RELEASED %
0
200
400
600
800
1000
1200
TIME (min)
-O- IMMEDIATE RELEASE
-□- SRC I
-Δ- SRC II

FIGURE 1

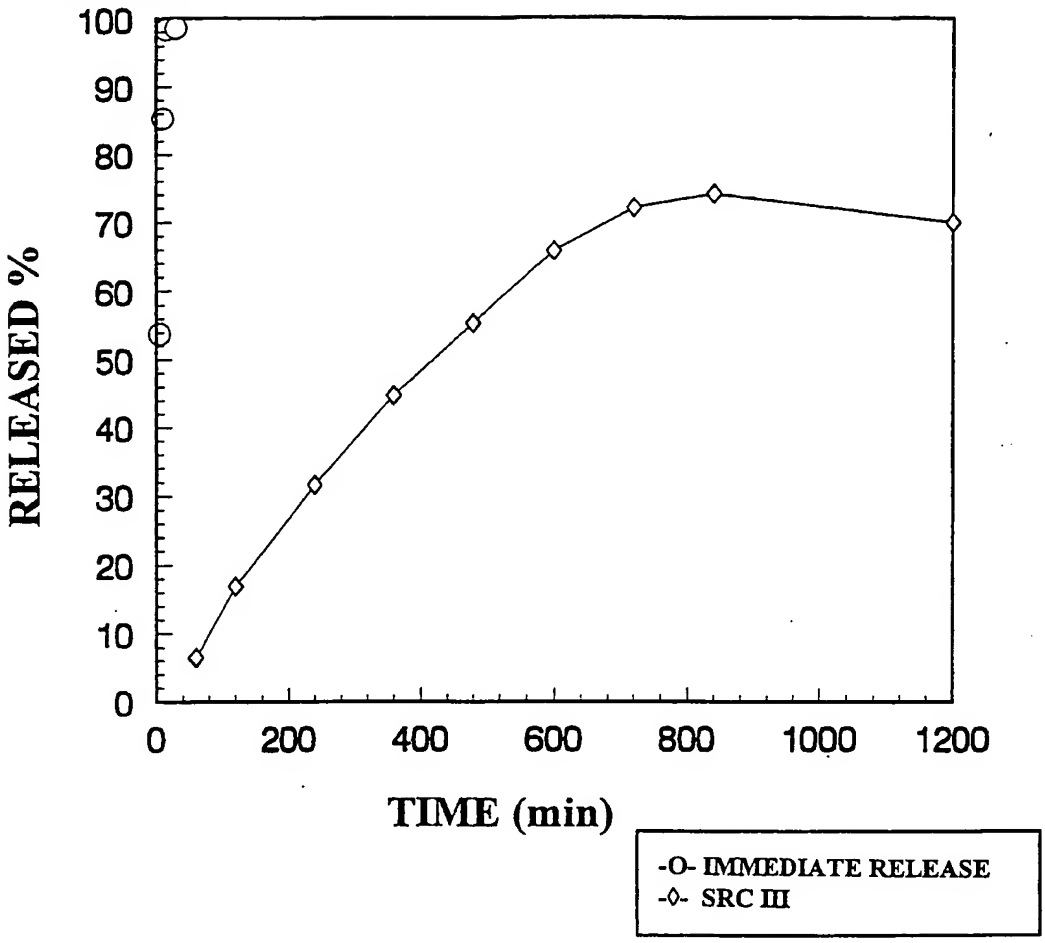
RELEASED %
100
90
80
70
60
50
40
30
20
10
0
0
200
400
600
800
1000
1200
TIME (min)
-O- IMMEDIATE RELEASE
-◊- SRC III

FIGURE 2